May 29, 2012

Ms. Jane Axelrad
Director, Office of Regulatory Policy
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
WO51, Room 6216
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

RE: Food and Drug Administration: Docket Number FDA-2012-D-0081; Draft Guidance on Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs

Dear Ms. Axelrad:

The Coalition for PET Drug Approval was organized in November 2010 to help the PET community understand requirements related to the implementation of 21 CFR part 212, and to communicate with the FDA on behalf of this community. It is within this capacity that we write to you in response to the request for comments on DRAFT GUIDANCE for Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs as published in the Federal Register on February 14, 2012, and we thank you for this opportunity.

Based on the discussion last March 2011 at the FDA Stakeholders meeting, our understanding was that the expanded access IND would be the preferred method for regulation of radiotracers that were not going forward for an NDA, e.g. C-11 Acetate and C-11 Methionine which have a half-life of 20 minutes and cannot be made available outside the institution producing them. They may be utilized for many years on an unknown number of patients. At that time there was no discussion of patient or time limitations under the expanded access mechanism.

According to the expanded access IND guidance the “current thinking” of the FDA limits the number of patients and the amount of time that the expanded access IND may be held by the physician investigators. Those sites wishing to use the radiotracer clinically would apply for expanded access IND authorization with the thought that the tracer would be used on an ongoing basis on any number of patients. Our concern is that it will be difficult provide clinical access to these radiotracers given the current time and patient number limitations. There is some difference in our understanding from the March 2011 meeting and the current expanded access IND verbage.

We include here a specific example to illustrate the importance of patient numbers and expanded time interval required to provide a radiotracer for clinical use.
1. SECTION VI. EXPANDED ACCESS FOR CLINICAL USE OF CERTAIN PET DRUGS

C. Types of Expanded Access Appropriate for PET Drugs

Line 437 ... Under this type of IND, FDA typically authorizes use prospectively in a pre-specified number of patients (eg. 10 to 20). If that number is reached, the sponsor can then ask FDA to authorize use in additional patients...

As an example: the Expanded Access IND was recommended as a method to use in order to proceed with using C-11 Acetate in the diagnosis of prostate cancer clinically at the University of Kansas. They are currently studying about 80 patients per year, and have evaluated a total of approximately 250 patients to date. They are charging to cover the cost of the study. Several insurance companies have been willing to pay for the cost of the C-11 acetate imaging study. The responsible physician contacted Lucie Yang, and she indicated that he should submit an expanded access IND. They plan to use this IND for several years then eventually conduct a prospective clinical trial looking at the biopsy-proven sensitivity and specificity of [11C] acetate PET/CTAC in recurrent prostate cancer.

Background:
In the spring of 2007, the physician investigator wanted to prove that [11C]acetate held the promise of superiority over ProstaScint, the only agent currently FDA-approved. He started with a clinical trial of 20 men status post radical prostatectomy with biochemical recurrent prostate cancer manifest by a PSA that had risen from 0.00 ng/dl post-operatively to greater than 0.2 ng/dl. He then imaged each of the 20 men with both [11C] acetate and ProstaScint within a two week period. The physician investigator referenced his findings in a monograph written for the Urological Clinics of North America last summer. They found for recurrences, with a mean size of 1 cm and a median PSA of 1.03 ng/ml, the putative sensitivity for [11C]acetate was 85% and for ProstaScint was only 30%. This seemed like a strikingly high difference, but the original ProstaScint data, noted that the best study showed only a 49% sensitivity and an accuracy of 63%. More importantly, most of the early studies on which FDA approval was given were performed with PSAs in the range of 4 to 8 ng/dl and tumor sizes ranging from 2 to 4 cm.

Having shown that high degree of sensitivity for [11C]acetate, he then started to offer the exam to referring urologists. From September 2008 until September 2011 when they were forced to shut the cyclotron down due to pending regulatory costs, they performed 250 studies utilizing [11C]acetate PET/CTAC. They are currently retrospectively analyzing the clinical data, specifically looking to see what variables are predictive for a positive exam so they can help advise clinicians when the
optimum time to study their patients. That is, is there a threshold PSA, such as 1.4 ng/ml or a PSA doubling time such as six months, that would assure a higher probability of finding metastases that would still be early enough to effect a remission if, for example, radiation tomotherapy were to be employed?

They are currently applying for an expanded access IND for [11C]acetate, a drug that has been used safely and effectively for more than twenty years in nuclear cardiology and for 5 years by the physician-investigator, so that they can prospectively study 250 patients with better control of the clinical data, looking at the effect of [11C]acetate PET/CTAC findings on clinical decision making.

We would respectfully ask the FDA to consider adding specific language to the Expanded Access IND guidance section to allow a variable number of patients, depending on the definition of the project, and use over multiple years with appropriate reporting to the FDA.

Thank you for the opportunity to review and comment on the Draft Guidance for Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs. Should you have any questions, please contact Janette Merrill, Associate Director, Health Policy and Regulatory Affairs, Society of Nuclear Medicine at jmerrill@snm.org or (703) 652-6760.

Sincerely,

Henry VanBroocklin
Co-Chair
Coalition for PET Drug Approval

Sally Schwarz
Co-Chair
Coalition for PET Drug Approval